
Reviews/Analyses

Clinical trials of improved oral rehydration salt formulations: a review

M.K. Bhan,¹ D. Mahalanabis,² O. Fontaine,³ & N.F. Pierce³

Reviewed are all the published clinical trials of glycine-based oral rehydration salts (ORS), L-alanine-based ORS, L-glutamine-based ORS, maltodextrin-based ORS, and rice-based ORS, as well as the results of several recently completed, but unpublished, studies of these formulations that were supported by WHO. All experimental ORS formulations contained the same concentrations of salts as citrate-based WHO-ORS; all trials were randomized comparisons with WHO-ORS, and all except those with rice-based ORS were double-blind studies. The rate of stool loss and, less frequently, the duration of diarrhoea were used as indicators of clinical performance to compare ORS formulations.

The following conclusions were reached concerning the efficacy and use of modified ORS formulations. Rice-based ORS (50 g/l) is superior to WHO-ORS for patients with cholera, and for such patients it can be recommended in any situation where its preparation and use are practical. Rice-based (50 g/l) and WHO-ORS solutions are equally effective for treating children with acute non-cholera diarrhoea, when feeding is resumed promptly following initial rehydration, as has been consistently recommended by WHO. Since rice-based ORS is not superior to WHO-ORS for such children, there is no apparent reason to advise a change from glucose to pre-cooked rice in the recommended formulation for WHO-ORS. Maltodextrin-based ORS formulations (50 g/l) and WHO-ORS appear to be equally effective for treating children with acute non-cholera diarrhoea; there is no reason to advise a change from glucose to maltodextrin in the recommended formulation for WHO-ORS. Amino-acid-containing ORS formulations are not recommended for either non-cholera or cholera diarrhoea, since they are more costly and have no clinical advantage over WHO-ORS for children with acute non-cholera diarrhoea or over rice-based ORS for persons with cholera.

Introduction

The oral rehydration salts (ORS) solution recommended by WHO is safe and effective for treating patients of all ages suffering from dehydration due to diarrhoea of any etiology, provided they are able to drink and that the dehydration is not severe (1). However, dehydration is an unusual event and

parents may not understand the relation between diarrhoea and the need for hydration. In any case, the parents' primary concern, which is often shared by many health workers, is to see the diarrhoea stop. This may limit the acceptance of the WHO-ORS solution as a "treatment" for diarrhoea, since it neither reduces the rate of stool loss nor shortens the duration of diarrhoea (2-5). In part, this may explain, the continuing widespread use of ineffective, and sometimes dangerous, "antidiarrhoeal" drugs and antibiotics.

These considerations have prompted efforts to develop an ORS formulation that, like WHO-ORS, would be inexpensive, safe, effective and stable during prolonged storage, but would also reduce the rate of stool loss and the duration of diarrhoea. Such a product could be promoted as having antidiarrhoeal activity and should therefore have greater acceptability; it might also help to reduce demand for ineffec-

¹ Additional Professor, Department of Pediatrics, All India Institute for Medical Sciences, New Delhi, India.

² Associate Director, Clinical Sciences Division, International Centre for Diarrhoeal Diseases Research, Bangladesh, Dhaka, Bangladesh.

³ Medical Officer, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to Dr O. Fontaine at this address.

tive antidiarrhoeal drugs. Such an achievement would represent a significant advance in efforts to control diarrhoea morbidity and mortality through effective case management.

Several approaches have been taken to develop such an improved ORS formulation. The present review describes the strategies used and summarizes the results of clinical trials of experimental formulations in adults and children suffering from dehydration caused by cholera or acute non-cholera diarrhoea.

Approaches taken to develop an improved ORS formulation

The effectiveness of the WHO-ORS solution depends on the coupled active transport of sodium ions and glucose across the brush border membranes of enterocytes (6), which results in passive absorption of water and other electrolytes. This function remains largely intact during diarrhoea, irrespective of its cause.

Two types of organic solutes are absorbed efficiently and relatively independently of each other in the small intestine, and each enhances the absorption of sodium ions and water: certain neutral amino acids—glycine, L-alanine, L-glutamine—and the dipeptides, tripeptides, proteins, and hydrolysed proteins from which they are derived; and glucose and the disaccharide (maltose), trisaccharide (maltotriose), oligosaccharide mixtures (maltodextrins of various grades), and polysaccharides (starches from rice or other cereals) from which glucose is derived.

One approach to developing an improved ORS formulation was based on adding neutral amino acids or their dipeptides to WHO-ORS (7). Glycine was studied first because of its low cost and low toxicity (8). Subsequently, L-alanine was used when it was discovered that it enhanced the transport of sodium ions across the brush border membrane more efficiently than glycine or glycyl-glycine (9). Recently, L-glutamine has been used because it enhances the absorption of both sodium and chloride ions (10); also, it is the principal metabolic fuel of the small bowel mucosa and is involved in the repair of mucosal damage (11, 12).

A second approach was to replace the glucose in ORS with glucose polymers, such as maltodextrins or cooked cereal powders, thus increasing the amount of potentially available glucose in the ORS solution, while decreasing its osmolality. The maximum concentration of glucose that can be employed in solutions of ORS salts is about 20 g/l (110 mmol/l); higher concentrations make the solution hypertonic and may cause osmotic diarrhoea. This amount is

only sufficient to promote the absorption of the sodium (90 mmol/l) and water in the ORS solution. Water and salts secreted into the intestine are not reabsorbed and the rate of stool loss is essentially unchanged (13). It was hypothesized that ORS formulations in which glucose (20 g/l) was replaced by increased amounts of maltodextrin or cooked rice powder (50–80 g/l) would be hypotonic, thus avoiding osmotic diarrhoea, but would yield sufficient glucose to promote also the reabsorption of endogenous intestinal secretions and thus reduce the volume and duration of diarrhoea (7).

A third approach combined the first two strategies: glucose polymers were used to provide a larger amount of glucose than in WHO-ORS, while reducing osmolality, and an amino acid (glycine) was added in an attempt to enhance further the absorption of sodium ions and water.

Results of clinical trials of experimental ORS formulations

Covered in the present review are data on all the published trials of glycine-based ORS, L-alanine-based ORS, L-glutamine-based ORS, maltodextrin-based ORS and rice-based ORS, as well as the results of several recently completed, but unpublished, studies of these formulations that were supported by WHO. All the experimental ORS formulations contained the same concentrations of salts as the citrate-based WHO-ORS; all trials were randomized comparisons with WHO-ORS; and all except those with rice-based ORS were double-blind.

We used the stool volume and, less frequently, the duration of diarrhoea as indicators of clinical performance to compare ORS formulations. However, each of these parameters independently affects the total stool output during an episode of diarrhoea. When both are reduced, for example, the percentage reduction in total stool output is usually greater than the percentage reduction in either of the contributing measurements. Therefore, total stool output during a diarrhoeal episode was considered to be the single most useful outcome measure for comparing different ORS formulations.^a

ORS solutions with added amino acids

Glycine-containing formulations. The first studies of glycine-containing ORS involved adults (14) and children (15) with acute diarrhoea caused mostly by

^a Recent advances in the development of improved ORS. Unpublished document WHO/CDD/CMT/91.1, 1991.

Vibrio cholerae O1 or enterotoxigenic *Escherichia coli* (ETEC). These reported that the addition of glycine (110 mmol/l) to WHO-ORS solution caused significant reductions in total stool volume and duration of diarrhoea (by 50% and 30%, respectively). However, the results of initial studies of a glycine-containing ORS solution (WHO-ORS solution containing an additional 110 mmol/l of glycine) in children with acute non-cholera diarrhoea were inconclusive: two studies reported a clinical benefit (16, 17), whereas four others showed no clinical advantage for the formulation with added glycine (18–21).

In an effort to clarify these findings, six glycine-containing ORS formulations were evaluated in nine clinical trials that were supported by WHO (22–27; and K.N. Jalan, H. Romer, E. Salazar-Lindo, personal communications). Subjects were children with acute non-cholera diarrhoea of viral or bacterial etiology. Only one study admitted children up to 5 years of age; otherwise the upper age limit was 2 years or 3 years. The criteria for inclusion and exclusion in the studies were similar. Several strategies were used to keep the osmolality of the experimental ORS formulations close to that of the WHO-ORS solution (311 mosmol/l). These included the following: reducing the glucose content of the solution; providing part of the amino acid as a dipeptide (glycyl-glycine); and replacing glucose by a glucose polymer (maltodextrin). The mean theoretical osmolality of the experimental solutions was 343 mosmol/l (range, 326–387 mosmol/l) (Table 1).

A meta-analysis of the results of seven of these trials, which included 643 subjects, has appeared (28). Two clinical trials that did not use the same standard recording forms were not included, although their results were similar to those of that meta-analysis (25; E. Salazar-Lindo, personal communication). The meta-analysis clearly showed that

the ORS formulations containing glucose (or maltodextrin) and glycine (or glycyl-glycine) were not clinically superior to the standard WHO-ORS solution. Rather, the total stool output was increased by 4% (95% confidence interval (CI) = –6%, 14%) and the duration of diarrhoea was increased by 3% (95% CI = –7%, 13%) with glycine-containing ORS solutions. Neither of these differences, however, was statistically significant.

L-Alanine-containing formulations. Three ORS formulations containing L-alanine have been tested in five clinical trials (29, 30; and P. Santos-Ocampo, A. Madkour, F.C. Patra, personal communications). The key features and results of these trials are summarized in Table 2. One study involved adults with cholera (29); another involved adults with diarrhoea of mixed etiology (cholera and non-cholera diarrhoea); and the other three were of under-5-year-olds with acute non-cholera diarrhoea caused mostly by rotavirus and ETEC.

Two studies using the same experimental formulation, containing 111 mmol/l of glucose and 90 mmol/l of L-alanine (400 mosmol/l), gave different clinical results in adults with cholera and children with acute non-cholera diarrhoea. This formulation was substantially more effective than WHO-ORS solution in patients with cholera (29), the total stool output being reduced by 42%. The same formulation, however, had no significant beneficial effect on stool output or duration of diarrhoea in children with acute non-cholera diarrhoea (30) (Table 2).

The other three studies of children with non-cholera diarrhoea and of adults with diarrhoea of mixed etiology used experimental formulations with a lower concentration of L-alanine (50 mmol/l), while two also used a lower amount of glucose (12 g/l or 18 g/l). Although the differences observed between the two treatment groups in the study

Table 1: Characteristics of the seven clinical trials with glycine-containing ORS solutions for non-cholera diarrhoea

Author	Year	Age of subjects (years)	Carrier substances in formulation	Solution osmolality (mosmol/l)	No. of patients
Santos Ocampo (ref. 22)	1988	<3	Glucose (20)/glycine (4)/glycyl-glycine (4)	387	66
Jalan	1988	<5	Maltodextrin MD25 (20)/glycine (4)/glycyl-glycine (4)	326	33
Römer	1988	<3	Maltodextrin MD25 (20)/glycine (4)/glycyl-glycine (4)	326	150
Pizarro et al. (ref. 23)	1988	<2	Glucose (12)/glycine (4)/glycyl-glycine (4)	342	62
Kassem et al. (ref. 27)	1989	<3	Maltodextrin MD25 (20)/glycine (4)/glycyl-glycine (4)	356	150 ^b
Kassem et al. (ref. 27)	1989	<3	Maltodextrin MD25 (20)/glycine (4)/glycine (8)	356	150 ^b
Bhan et al. (ref. 24)	1990	<2	Maltodextrin MD25 (20)/glycine (4)/glycyl-glycine (4)	326	93
Grange (ref. 26)	1992	<3	Maltodextrin MD25 (20)/glycine (8)	356	89

^a Figures in parentheses are the substance concentrations in g/l.

^b Three-cell study comparing two experimental formulations with WHO-ORS solution (50 patients per cell).

involving adults were not statistically significant, the L-alanine-containing ORS solution reduced the total stool output by 22%. On the other hand, in the studies involving children, although the osmolarities of these formulations (360–320 mosmol/l) were closer to that of the WHO-ORS solution (311 mosmol/l), the experimental ORS formulations exhibited no clinical advantage over WHO-ORS (Table 2).

L-Glutamine-containing formulation. Three clinical trials of an L-glutamine-containing ORS have recently been completed (62 and R. Kumala, M.K. Bhan, personal communications). The first involved adults with cholera, while the other two involved children with acute non-cholera diarrhoea.

The key features and results of these trials are given in Table 3. The study of the adults with cholera used an experimental formulation containing 90 mmol/l of glucose and 90 mmol/l of L-glutamine (380 mosmol/l). The two studies of children with non-cholera diarrhoea used an experimental formulation containing 50 mmol/l of glucose and 50 mmol/l of L-glutamine (300 mosmol/l).

The clinical effectiveness of the L-glutamine-containing ORS solutions was similar to that of glycine- and L-alanine-containing ORS formulations: for the adults with cholera, there was a significant reduction in the stool output and duration of diarrhoea but no clinical advantage over the WHO-ORS solution for the children with non-cholera diarrhoea, although the total osmolarity of the solution was slightly less than that of the WHO-ORS solution.

Cereal-based ORS formulations

Numerous trials comparing cereal-based ORS formulations with WHO-ORS have been reported. Most

have involved rice-based formulations but a few have involved other cereals such as sorghum-wheat- or maize-based ORS. The results obtained with these other cereals generally resemble those obtained with rice-based ORS. Consequently, only the results of the clinical trials of rice-based ORS are reviewed here. These have been divided into the following categories:

- thirteen trials summarized in a previously reported meta-analysis (31);
- two recently completed trials (42, and A.M. Molla, personal communication); and
- additional studies involving subjects of special concern: infants below 6 months of age (63); severely malnourished children (43); and children with a high prevalence of glucose malabsorption (E. Chea-Woo, personal communication).

These are discussed in detail below.

Meta-analysis of 13 clinical trials. Several early trials showed that ORS solutions containing 50–80 g/l of cooked rice powder in place of the 20 g/l of glucose in the WHO-ORS solution substantially reduced the rate of stool loss during episodes of acute diarrhoea (32–36). Other studies, however, reported no significant benefit for the rice-based ORS (37–40). Interpretation of these results is difficult because of the wide age range of the study subjects, differences in the practices (food was offered at various intervals after rehydration, often not until 24 or 48 hours later, or feeding practices were not described). Additionally, total stool output and duration of diarrhoea were reported in only one trial, although all studies reported the initial 24-hour stool output.

Table 2: Characteristics and results of the clinical trials with alanine-containing ORS solutions

Author	Year	Patients	Carrier substances (g/l)		Solution osmolarity (mosmol/l)	No. of patients	% difference in: ^{a, b}	
			Glucose	Alanine			Mean total stool output	Mean diarrhoea duration
Patra et al. (ref. 29)	1989	Cholera (adults)	20	8	400	94	–42 (–62 to –21) ^c	–15 (–27 to 0)
Patra	1993	Cholera and non-cholera (adults)	18	4.5	350	154	–22 (–46 to 3)	–9 (–19 to 1)
Sazawal et al. (ref. 30)	1991	Non-cholera (<3 years of age)	20	8	400	129	–2 (–39 to 35)	–5 (–14 to 17)
Santos Ocampo	1991	Non-cholera (<3 years of age)	20	4.5	360	140	23 (–21 to 69)	8 (–15 to 31)
Madkour	1991	Non-cholera (<3 years of age)	12	4.5	320	100	–18 (–48 to 12)	–11 (–33 to 5)

^a [(Alanine-containing ORS – glucose ORS)/glucose ORS] × 100.

^b % difference in stool output and duration of diarrhoea refers to the reduction with the experimental ORS solution when the sign is negative.

^c Figures in parentheses are the 95% confidence interval.

Table 3: Characteristics and results of clinical trials with glutamine ORS solutions

Author	Year	Patients	Carrier substances (g/l)		Solution osmolality (mosmol/l)	No. of patients	% difference in: ^{a, b}	
			Glucose	Alanine			Mean total stool output	Mean diarrhoea duration
Kumala	1991	Cholera (adults)	16	13	355	181	-30 (-34 to 28) ^c	-13 (-24 to 2)
Bhan	1992	Non-cholera (<3 years of age)	9	7.3	300	125	-1 (-33 to 30)	14 (-8 to 36)
Ribeiro et al. (ref. 62)	1992	Non-cholera (<3 years of age)	9	7.3	300	118	3 (-26 to 32)	1 (-16 to 19)

^a [(Glutamine-containing ORS-glucose ORS)/glucose ORS] × 100.

^b See footnote b, Table 2.

^c Figures in parentheses are the 95% confidence interval.

To clarify these results, a meta-analysis was carried out in 1992 of all published or available randomized controlled trials comparing rice-based ORS (50–80 g/l) with WHO-ORS (37). A total of 13 studies were evaluated (32–41: A.M. Moechtar, E. Guiraldes, A.N. Alam, personal communications). These involved 531 adults and 424 children with cholera or severe cholera-like diarrhoea, and 344 infants and young children with acute non-cholera diarrhoea. The key features of the studies analysed are given in Table 4. In some studies, rice powder was cooked immediately before use and the salts then added; in others, packets containing pre-cooked rice powder and ORS were used.

The meta-analysis showed that, irrespective of their age, cholera patients given rice-based ORS solution had substantially lower rates of stool loss than those given WHO-ORS solution. Stool output was reduced by a mean of 55 g per kg during the first 24 hours of treatment with rice-based ORS solution, a reduction of 34% (95% CI = 25%, 43%). In contrast, the initial 24-hour stool output of children with acute non-cholera diarrhoea and who were given rice-based ORS solution was only reduced by a mean of 18 g per kg (18%); 95% CI = 6%, 30%), relative to children given WHO-ORS solution.

Recently completed trials. Two recently completed studies were designed to address the weaknesses identified in the above trials, especially the impact of early feeding, as recommended by WHO, on the effectiveness of both the glucose-based ORS solution and the rice-based ORS solution (42; A.M. Molla, personal communication).

The trials included 611 under-18-month-olds with acute non-cholera diarrhoea and signs of moderate dehydration. Children who were predominantly breast-fed or with severe malnutrition were excluded. The children were offered a standard rice and vegetable diet in six to eight helpings of equal volume (150 g per kg per day) starting immediately

after completion of rehydration (usually 4–6 hours). Data on total stool output and duration of diarrhoea were available for all but a few of the randomized patients. The key features and results of these trials are summarized in Table 5.

In both studies, the 24-hour stool output, total stool output, and duration of diarrhoea were marginally reduced among patients given standard WHO-ORS solution compared with those given rice-based ORS solution. None of these differences was statistically significant, however, except the duration of diarrhoea, which, in one study (42), was significantly shorter among patients given WHO-ORS solution.

Studies involving subjects of special concern

Infants below 6 months of age. Because pancreatic amylase is deficient at birth and does not reach adult levels until about 5 months of age, rice-based ORS solution may not be suitable for use with very young infants. This has been examined in a recent trial comparing rice-based ORS and standard WHO-ORS solutions in 100 infants below 6 months of age with acute diarrhoea (63). No significant differences were observed between treatment groups with regard to total stool output and duration of diarrhoea. The total stool output was reduced by 16% (95% CI = -13%, 55%) and the duration of diarrhoea by 8% (95% CI = -26%, 42%) with rice-based ORS solution. Since the confidence intervals for these comparisons include zero, they are not statistically significant.

Infants with severe malnutrition. Children with severe malnutrition may also be deficient in pancreatic amylase, which raises concern about the safety and efficacy of treating them with rice-based ORS solution. In a recently published evaluation of rice-based ORS solution in 150 severely malnourished children with acute non-cholera diarrhoea, no significant differences were observed in total stool output

Table 4: Characteristics of the clinical trials of rice-based ORS included in the initial meta-analysis

Author	Year	Age of patients (years) ^a	Amount of rice in ORS (g/l)	No. of patients
<i>Cholera or cholera-like illness</i>				
Moechtar ^b	1989	>12	50	164
Moechtar ^b	1989	>12	50	26
Alam ^c	1991	Adults	50	93
Alam ^c	1991	Adults	50	89
Molla et al. (ref. 34)	1985	>10	80	157
Molla et al. (ref. 34)	1985	<10	80	185
Molla et al. (ref. 36)	1989	<5	50	79
Molla et al. (ref. 33)	1983	<5	80	52
Alam et al. (ref. 35)	1985	<8	50	39
Alam et al. (ref. 35)	1985	<8	50	13
Patra et al. (ref. 32)	1982	<5	50	52
<i>Acute non-cholera diarrhoea</i>				
Guiraldes	1991	<2	50	97
Dutta et al. (ref. 38)	1988	<4	50	70
Bhan et al. (ref. 37)	1987	<5	50	64
El Mougi et al. (ref. 41)	1988	<1.5	50	51
Mohan et al. (ref. 39)	1985	<3	50	46

^a None of the studies included infants aged <3 months.^b Single studies in which results were stratified for analysis.^c Clinical trial with a factorial design (4-cell trial).

for patients treated with rice-based ORS or WHO-ORS solutions (43). Total stool output was reduced by 13% (95% CI = -15%, 41%) with rice-based ORS solution but this was not statistically significant.

Children with an increased risk of glucose malabsorption. A study conducted in Peru reported that glucose malabsorption, leading to an increased rate of treatment failure during oral rehydration therapy, occurred frequently (44). Based on previous studies, the rate of treatment failure due to clinically evident glucose intolerance in young children with acute

non-cholera diarrhoea was expected to be no more than 2% (45-50). However, in the Peruvian study, 30% of the patients aged 3-24 months had detectable glucose malabsorption leading to treatment failure in 7% (the proportion of patients requiring intravenous therapy after rehydration was completed), well in excess of the expected 2% failure rate.

The safety and efficacy of rice-based ORS solution was evaluated in a study involving children from a similar population with a high prevalence of glucose malabsorption (E. Chea-Woo, personal communication). A total of 45% of patients admitted to the study had detectable glucose malabsorption,

Table 5: Results of recently completed clinical trials of rice-based ORS in young children with non-cholera diarrhoea who were offered optimal feeding early in the illness

Author	Year	No. of patients	Age of patients (months)	% difference in: ^{a, b}	
				Mean total stool output	Mean diarrhoea duration
Fayad et al. (ref. 42)	1993	441	3-18	17 (-4 to 37) ^c	25 (10 to 41)
Molla	1993	170	3-12	19 (-20 to 57)	2 (-22 to 25)

^a [(Rice ORS - glucose ORS)/glucose ORS] × 100.^b See footnote b, Table 2.^c Figures in parentheses are the 95% confidence interval.

defined as the presence of >1% glucose in the stools and stool pH <5.5. However, no significant differences were observed in the total stool output or in the duration of diarrhoea with the rice-based ORS solution. Treatment failure rates were high, but not significantly different between treatment groups (24% for patients treated with rice ORS solution versus 27% for those treated with WHO-ORS solution).

Revised meta-analysis of rice-based versus WHO-ORS solution. The results of these recently completed clinical trials, involving 828 non-severely malnourished infants and young children with acute non-cholera diarrhoea in which the WHO-ORS solution was compared with the rice-based ORS solution, were combined with the results of the five studies conducted on 344 similar children and already presented in the 13-study meta-analysis (31). The revised meta-analysis, the results of which are summarized in Fig. 1, therefore took into account nine studies and included a total of 1172 children. The results indicate that stool output was reduced by 7% (95% CI = -3%, 15%) for patients receiving rice-based ORS solution compared with those receiving standard glucose-containing ORS solution; this difference was not statistically significant.

Maltodextrin-based ORS formulation

These studies were prompted by the initially encouraging results reported with rice-based ORS. Maltodextrins were considered to be an attractive alternative to cooked rice powder for the following reasons: they are glucose polymers with low osmotic activity; they dissolve easily in water without cooking; they are inexpensive; and they could easily replace glucose in packaged ORS (53-55).

An ORS formulation containing 50 g/l of minimally hydrolysed maltodextrin (MD02) (227 mosmol/l) in place of glucose was evaluated in four clinical trials involving young children with acute non-cholera diarrhoea (51, 52 and K.N. Jalan, M. El-Mougi, personal communications). The key features and results of these trials are shown in Table 6.

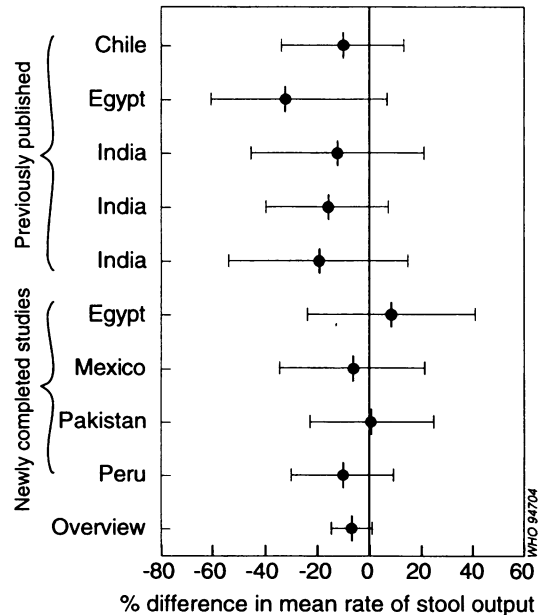
The efficacy of maltodextrin-based ORS was similar to that of WHO-ORS. There was no significant beneficial effect of maltodextrin-based ORS on either total stool output or duration of diarrhoea.

Discussion

Role of clinical trials in evaluation of ORS formulations

The clinical efficacy of an ORS formulation is determined by the extent to which the water and electrolytes it contains are absorbed from the intestine. This

Fig. 1. Mean percentage reduction in 24-hour stool output among individual studies of children with non-cholera diarrhoea given rice-based ORS solution compared with children given WHO-ORS solution. $\left(\frac{\text{Rice ORS} - \text{glucose ORS}}{\text{glucose ORS}} \times 100\right)$. The pooled (weighted) estimate of percentage reduction in mean stool output (95% confidence interval) is shown under "overview".



can only be determined using controlled clinical trials involving patients with diarrhoea in which oral intake and faecal output of water and electrolytes are carefully measured.

Two processes within the intestine determine the efficacy of an ORS formulation. The first is rapid osmotic equilibration of the ingested solution with extracellular fluid, which occurs mostly in the duodenum and proximal jejunum (56) and results from the flow of water across the semipermeable bowel mucosa. Water is absorbed from hypotonic ORS solutions and added to solutions that are hypertonic. The second is absorption of water and electrolytes that is mediated by actively absorbed organic molecules, such as glucose and certain amino acids. This occurs throughout the small bowel (2, 3). In addition, when metabolized by colonic bacteria, undigested starch entering the colon, produces short-chain fatty acids that stimulate electrolyte absorption in the colon (57).

Although experimental studies of absorption from intestinal segments in humans or animals, or *in-vitro* systems, can help to guide the design of clinical

Table 6: Results of clinical trials of maltodextrin ORS with non-cholera patients

Author	Year	No. of patients	Age of patients (months)	% difference in: ^{a, b}	
				Mean total stool output	Mean diarrhoea duration
Akbar et al. (ref. 51)	1991	69	<36	-10 (-73 to 52) ^c	-8 (-37 to 22)
Santos Ocampo et al. (ref. 52)	1993	116	<36	35 (-26 to 51)	-8 (-31 to 15)
El Mougi	1990	89	<24	23 (-32 to 46)	-9 (-42 to 60)
Jalan	1990	32	<36	-25 (-85 to 36)	-5 (-71 to 81)

^a [(Maltodextrin ORS – glucose ORS)/glucose ORS] × 100.

^b See footnote b, Table 2.

^c Figures in parentheses are the 95% confidence interval.

trials and interpret their outcome, they cannot determine the combined effect of the processes listed above on net absorption throughout the length of the gut and, thus, cannot replace clinical trials or necessarily predict their outcome. Moreover, most such studies are performed with healthy intestine and the few available models of infection-induced intestinal secretion do not parallel the full range of etiological agents or pathogenic processes that cause diarrhoea and for which ORS solutions are used.

Efficacy of modified ORS formulations in cholera

The clinical trials summarized in this review show that the efficacy of experimental ORS formulations depends on the etiology of diarrhoea but not on the age of the subjects. Both amino-acid-containing and rice-based formulations were superior to WHO-ORS for adults and children with cholera. The superior performance of these solutions was manifested by substantially reduced rates of stool output, duration of diarrhoea, and total diarrhoeal stool volume.

For patients with cholera, similar clinical benefits occurred with solutions that were either hypotonic (rice-based ORS solution: ca. 200 mosmol/l) or hypertonic (amino-acid-containing ORS solutions: 360–421 mosmol/l) relative to WHO-ORS solution (311 mosmol/l). The improved performance of the amino-acid-containing solutions indicates that the absorption-promoting effect of added amino acids exceeds the potentially adverse effect of hypertonicity, which would initially cause a flow of water from the blood into the bowel lumen, increased luminal fluid volume and, if the ORS solution and added water were not eventually absorbed, increased stool volume. The net benefit of these solutions would not have been evident from animal studies that point to

the dangers of hypertonic solutions and the benefits of hypotonic solutions (58, 59).

In contrast, the clinical benefit of rice-based ORS was probably due to its hypo-osmolality, which would enhance water absorption, and to its potential to release more glucose than WHO-ORS without incurring an “osmotic penalty” (7, 60). The possibility that amino acids released from the digestion of proteins in rice powder also contributed to the efficacy of rice-based ORS cannot be excluded.

Efficacy of modified ORS formulations in acute non-cholera diarrhoea

The results of studies of children with acute non-cholera diarrhoea differed markedly from those of adults or children with cholera. Amino-acid-supplemented solutions had no beneficial effect, and rice-based ORS solution had only a modest advantage over WHO-ORS solution, which disappeared when feeding with a normal cereal-based diet was resumed promptly after initial rehydration was completed. For young infants, children with severe malnutrition, and children with a high prevalence of glucose malabsorption, rice-based ORS solution had the same efficacy as WHO-ORS solution. Maltodextrin-based ORS had no beneficial effect over WHO-ORS solution.

Although the clinical trials summarized here were not designed to explore the mechanisms of action of different ORS solutions, comparison of these results with those for patients with cholera suggest that the pathogenic effects of agents causing non-cholera diarrhoea in young children prevented such solutions from having greater efficacy than WHO-ORS solutions. The most likely explanation for this is that the breakdown of polysaccharides or proteins, or the absorption of glucose or amino acids,

or both, was partially impaired in these children. Such effects might be greater if diarrhoea is caused by certain etiological agents, but this could not be determined. It is known, however, that the causative agents of acute non-cholera diarrhoea include several that invade or damage bowel mucosa (e.g., rotavirus, *Shigella* spp., enteropathogenic *E. coli*) and might be expected to have multiple effects on intestinal function. In contrast, *V. cholerae* O1 is not invasive and does not cause mucosal damage; cholera results almost entirely from the action of cholera toxin, which alters the normal processes for absorption of sodium and chloride ions by intestinal mucosa, but does not affect carrier-linked absorption of sodium ions (61).

It is of interest that rapid intestinal transit did not appear to limit the effectiveness of ORS solutions, since transit is most rapid in patients with cholera.

Proposed use of modified ORS formulations

Below are summarized the conclusions and recommendations concerning the use of modified ORS formulations.

- Rice-based ORS (50 g/l) is superior to WHO-ORS for patients with cholera. Its use for cholera patients can be recommended for any situation where its preparation and use are practical.
- Rice-based (50 g/l) and WHO-ORS solutions are equally effective for treating children with acute non-cholera diarrhoea, when feeding is resumed promptly following initial rehydration, as has been consistently recommended by WHO. Rice-based and WHO-ORS solutions are also equally effective for young infants, children with severe malnutrition, and children with an increased risk of glucose malabsorption. Since rice-based ORS is not superior to WHO-ORS for such children, there is no reason to advise a change from glucose to pre-cooked rice in the recommended formulation for WHO-ORS. Such a change would be very costly to implement and be without advantage, except for patients with cholera.
- Maltodextrin-based ORS formulations (50 g/l) and WHO-ORS appear to be equally effective for treating children with acute non-cholera diarrhoea. There is therefore no reason to advise a change from glucose to maltodextrin in the recommended formulation for WHO-ORS.
- Amino-acid-containing ORS formulations are not recommended for either non-cholera or cholera diarrhoea since they are more costly and have no clinical advantage over WHO-ORS for children with acute

non-cholera diarrhoea or over rice-based ORS for persons with cholera.

Acknowledgements

We thank Dr J. Tulloch for valuable comments and suggestions in the preparation of this paper, and Ms M. King for secretarial help.

Résumé

Formules améliorées de sels de réhydratation orale: le point

Cet article présente les résultats d'une revue de tous les essais cliniques publiés, ainsi que les résultats de plusieurs études récemment achevées mais non encore publiées, sur les sels de réhydratation orale (SRO) à base de glycine, de L-alanine, de L-glutamine, de maltodextrine ou de riz et qui ont été financés par le Programme de Lutte contre les Maladies diarrhéiques (LMD) de l'Organisation mondiale de la Santé (OMS). Les SRO expérimentaux, dont l'efficacité était évaluée dans ces études, contenaient les mêmes concentrations de sels que les SRO à base de citrate recommandés par l'OMS. Tous les essais cliniques étaient des comparaisons randomisées de SRO expérimentaux avec les SRO de l'OMS, et tous, à l'exception des essais de SRO à base de riz, étaient des études en double-insu. Le volume des selles et, moins fréquemment, la durée de la diarrhée, ont été utilisés comme indicateurs pour comparer l'efficacité clinique des différentes compositions de SRO. Cette revue a permis de tirer un certain nombre de conclusions quant à l'efficacité et l'utilisation de ces formules modifiées de SRO:

- Les SRO à base de riz (50 g/l) sont supérieurs aux SRO de l'OMS pour traiter les malades atteints de choléra; leur utilisation chez ces malades peut être recommandée dans toutes les situations où leur préparation et leur utilisation sont réalisables en pratique.
- Les SRO à base de riz (50 g/l) et les SRO de l'OMS ont la même efficacité pour le traitement des enfants présentant une diarrhée aiguë d'origine non cholérique, quand l'alimentation est redémarrée rapidement après la réhydratation initiale, comme cela est recommandé par l'OMS. L'efficacité des SRO à base de riz n'étant pas supérieure à celle des SRO de l'OMS, il n'y a aucune raison de recom-

mander le remplacement du glucose par le riz dans la composition des SRO de l'OMS.

- Les SRO à base de maltodextrines (50 g/l) et les SRO de l'OMS ont la même efficacité pour le traitement des enfants présentant une diarrhée aiguë d'origine non cholérique; il n'y a donc aucune raison de recommander le remplacement du glucose par des maltodextrines dans la composition des SRO de l'OMS.
- Les SRO à base d'acides aminés ne sont recommandés ni pour le traitement des diarrhées d'origine non cholérique, ni pour le traitement des choléras, car ils sont plus chers et n'offrent aucun avantage clinique par rapport aux SRO de l'OMS pour les enfants présentant une diarrhée aiguë d'origine non cholérique ou par rapport aux SRO à base de riz pour les personnes atteintes de choléra.

References

1. Avery ME, Snyder JD. Oral therapy for acute diarrhoea. The underused simple solution. *New England journal of medicine*, 1990, **323**: 891–894.
2. Pierce NF et al. Effect of intragastric glucose electrolyte infusion upon water and electrolyte balance in Asiatic cholera. *Gastroenterology*, 1968, **55**: 333–343.
3. Hirschhorn N et al. Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. *New England journal of medicine*, 1968, **279**: 176–180.
4. Mahalanabis D et al. Use of an oral glucose electrolyte solution in the treatment of pediatric cholera: a controlled study. *Journal of tropical pediatrics and environmental child health*, 1974, **20**: 82–87.
5. Sack SA et al. Oral hydration in rotavirus diarrhoea: a double-blind comparison of sucrose with glucose electrolyte solution. *Lancet*, 1978, **2**: 280–283.
6. Schultz SG. Sodium coupled solute transport by small intestine; a status report. *American journal of physiology*, 1977, **223**: E249–E254.
7. Mahalanabis D, Patra FC. In search of a super oral rehydration solution: can optimum use of organic solute mediated sodium absorption lead to the development of an absorption-promoting drug? *Journal of diarrhoeal diseases research*, 1983, **1**: 76–81.
8. Milne MD. Pharmacology of amino acids. *Clinical pharmacology and therapeutics*, 1968, **9**: 484–516.
9. Wapnir RA et al. Oral hydration solution (OHS): effectiveness of alanine in a model of osmotic diarrhoea. *Pediatric research*, 1986, **20**: 252A.
10. Souba WW, Smith RJ, Wilmore DW. Glutamine metabolism by the intestinal tract. *Journal of parenteral and enteral nutrition*, 1985, **9**: 608–616.
11. Askanazi J et al. Muscle and plasma amino acids following injury. Influence of intercurrent infection. *Annals of surgery*, 1980, **192**: 78–85.
12. Cersosimo E et al. Role of glutamine in adaptation in nitrogen metabolism during fasting. *American journal of physiology*, 1986, **259**: E622–E628.
13. Hirschhorn N. The treatment of acute diarrhoea in children: an historical and physiological perspective. *American journal of clinical nutrition*, 1980, **33**: 637–663.
14. Nalin DR et al. Effect of glycine and glucose on sodium and water absorption in patients with cholera. *Gut*, 1970, **11**: 768–772.
15. Patra FC et al. In search of a super solution: controlled clinical trial of a glycine glucose oral rehydration solution in infantile diarrhoea. *Acta paediatrica Scandinavica*, 1984, **73**: 18–21.
16. Bai NS, Arunambika, Philips E. A comparative study of Speedoral versus the WHO formula in acute diarrhoea in children. *Medicine and surgery*, 1988, **28**: 19–22.
17. Padmanabhan AS, Ganga N, Ashok TP. A controlled trial of glycine-supplemented oral rehydration solution (ORS) in childhood diarrhoea. *Physicians update*, 1988, **1**: 37–39.
18. Vesikari T, Isolauri E. Glycine-supplemented oral rehydration solutions for diarrhoea. *Archives of disease in childhood*, 1986, **61**: 372–376.
19. Santosham M et al. Glycine-based oral rehydration solution: reassessment of safety and efficacy. *Journal of pediatrics*, 1986, **109**: 795–801.
20. Briones M et al. [A saline solution containing oligosaccharides and glycine for oral hydration]. *Boletín medico del Hospital Infantil de Mexico*, 1988, **45**: 437–441 (in Spanish).
21. Carmuega E et al. [Clinical trial of a super oral hydration serum]. *Archives Argentinas de Pediatría*, 1987, **85**: 77–81 (in Spanish).
22. Santos Ocampo PD et al. Clinical trial on the efficacy and safety of added glycine and glycyl-glycine to oral rehydration solution. *Philippine journal of pediatrics*, 1988, **36**: 99–120.
23. Pizarro D et al. Comparison of efficacy of a glucose/glycine/glycyl-glycine electrolyte solution versus the standard WHO/ORS in diarrhoeic dehydrated children. *Journal of pediatric gastroenterology and nutrition*, 1988, **6**: 882–888.
24. Bhan M. et al. Glycine, glycyl-glycine and maltodextrin based oral rehydration solution. *Acta paediatrica Scandinavica*, 1990, **79**: 518–526.
25. Khin Maung U et al. Comparison of glucose/electrolyte and maltodextrin/glycyl-glycine/electrolyte oral rehydration solution in acute diarrhoea in children. *Journal of pediatric gastroenterology and nutrition*, 1991, **13**: 397–401.
26. Grange A. Evaluation of a maltodextrin/glycine oral rehydration solution. *Annals of tropical paediatrics*, 1992, **12**: 353–358.
27. Kassem AS et al. Glycine and glycyl-glycine enriched oral rehydration solutions in the management of infantile diarrhoea. *Alexandria journal of pediatrics*, 1989, **3**: 215–226.
28. International Study Group on Improved ORS. Impact of glycine-containing oral rehydration solutions on stool output and duration of diarrhoea: a meta-analysis of seven clinical trials. *Bulletin of the World Health Organization*, 1991, **69**: 541–548.
29. Patra FC et al. Oral rehydration formula containing alanine and glucose for treatment of diarrhoea: a controlled trial. *British medical journal*, 1989, **298**: 1353–1356.

30. **Sazawal S et al.** Alanine-based oral rehydration solution: an assessment of efficacy in acute non-cholera diarrhoea among children. *Journal of pediatric gastroenterology and nutrition*, 1991, **12**: 461–468.
31. **Gore SM, Fontaine O, Pierce NF.** Impact of rice-based oral rehydration solutions on stool output and duration of diarrhoea: a meta-analysis of 13 clinical trials. *British medical journal*, 1992, **304**: 287–291.
32. **Patra FC et al.** Is oral rice electrolyte solution superior to glucose electrolyte solution in infantile diarrhoea? *Archives of disease in childhood*, 1982, **57**: 910–912.
33. **Molla AM et al.** Rice-based oral rehydration therapy in acute diarrhoea: a superior therapy and a medium for calorie supplementation. In: Eeckles RE, Ransome-Kuti O, Kroonenberg CC, eds. *Child health in the tropics: Sixth Nutricia-Cow & Gates Symposium, Louvain, 18–21 October 1983*. Dordrecht, Nijhoff, 1985: 65–70.
34. **Molla AM, Ahmed SM, Greenough III WB.** Rice-based oral rehydration solution decreases the stool volume in acute diarrhoea. *Bulletin of the World Health Organization*, 1985, **63**: 751–756.
35. **Alam AN et al.** Hydrolysed wheat based oral rehydration solution for acute diarrhoea. *Archives of disease in childhood*, 1987, **62**: 440–444.
36. **Molla AM et al.** Food-based oral rehydration salt solution for acute childhood diarrhoea. *Lancet*, 1989, **2**: 429–431.
37. **Bhan MK et al.** Efficacy of mung bean and pop rice based oral rehydration solutions in comparisons with the standard glucose electrolyte solution. *Journal of pediatric gastroenterology and nutrition*, 1987, **6**: 392–399.
38. **Dutta P et al.** Comparative efficacy of three different oral rehydration solutions for the treatment of dehydrating diarrhoea in children. *Indian journal of medical research*, 1988, **87**: 229–233.
39. **Man Mohan et al.** Rice powder oral rehydration solution as an alternative to glucose electrolyte solution. *Indian journal of medical research*, 1988, **87**: 234–239.
40. **Kenya PP et al.** Cereal-based oral rehydration solutions. *Archives of disease in childhood*, 1989, **64**: 1032–1035.
41. **El Mougí M et al.** Controlled clinical trial on the efficacy of rice powder based oral rehydration solution on the outcome of acute diarrhoea in infants. *Journal of pediatric gastroenterology and nutrition*, 1988, **7**: 572–576.
42. **Fayad IM et al.** Comparative efficacy of rice-based ORS plus early feeding versus glucose-based ORS plus early feeding. *Lancet*, 1993, **342**: 772–775.
43. **Razafindrakoto O et al.** La solution de réhydratation orale (SRO) à base de riz, alternative de la SRO de l'OMS dans la diarrhée aiguë des malnutris. *Archives françaises de Pédiatrie*, 1992, **50**: 101–105.
44. **Salazar-Lindo E et al.** Bicarbonate versus citrate in oral rehydration therapy in infants with watery diarrhoea: a controlled clinical trial. *Journal of pediatrics*, 1986, **108**: 55–60.
45. **Nalin DR et al.** Comparison of low and high sodium and potassium content in oral rehydration solutions. *Journal of pediatrics*, 1980, **97**: 848–853.
46. **Clements ML et al.** Comparison of simple sugar/salt versus glucose/electrolyte oral rehydration solution in infant diarrhoea. *Journal of tropical medicine and hygiene*, 1981, **84**: 189–194.
47. **Sack DA et al.** Oral rehydration in rotavirus diarrhoea: a double-blind comparison of sucrose with glucose electrolyte solution. *Lancet*, 1978, **2**: 280–283.
48. **Black RE et al.** Glucose versus sucrose in oral rehydration solutions for infants and young children with rotavirus-associated diarrhoea. *Pediatrics*, 1981, **67**: 79–83.
49. **Santosham M et al.** Oral rehydration therapy of infantile diarrhoea: a controlled study of well nourished children hospitalized in the United States and Panama. *New England journal of medicine*, 1982, **306**: 1070–1076.
50. **Sack RB et al.** The use of oral replacement solutions in the treatment of cholera and other severe diarrhoeal disorders. *Bulletin of the World Health Organization*, 1970, **43**: 351–360.
51. **Akbar MS et al.** A randomized double-blind clinical trial of a maltodextrin containing oral rehydration solution in acute infantile diarrhoea. *Journal of diarrhoeal disease research*, 1991, **9**: 33–37.
52. **Santos Ocampo PD et al.** A randomized double-blind clinical trial of a maltodextrin containing oral rehydration solution in acute infantile diarrhoea. *Journal of pediatric gastroenterology and nutrition*, 1993, **16**: 23–28.
53. **Daum F et al.** Intestinal osmolality and carbohydrate absorption in rats treated with polymerized glucose. *Pediatric research*, 1978, **12**: 24–26.
54. **Kerzner B et al.** Jejunal absorption of short and long chain glucose oligomers in the absence of pancreatic amylase. *Pediatric research*, 1981, **15**: 250–253.
55. **Klish W et al.** The effect of intestinal solute load on water secretion in infants with acquired monosaccharide intolerance. *Pediatric research*, 1980, **14**: 1343–1346.
56. **Fordtran JS, Rector FC, Carter NW.** The mechanism of sodium absorption in the human small intestine. *Journal of clinical investigation*, 1968, **47**: 884–890.
57. **Bowling TE et al.** Reversal by short-chain fatty acids of colonic fluid secretion induced by enteral feeding. *Lancet*, 1993, **342**: 1266–1268.
58. **Lifschitz F, Wapnir RA.** Oral hydration solutions: experimental optimization of sodium and water absorption. *Journal of pediatrics*, 1985, **106**: 383–389.
59. **Wapnir RA, Lifschitz F.** Osmolality and solute concentration — their relationship with oral hydration solution effectiveness: an experimental assessment. *Pediatric research*, 1985, **19**: 894–898.
60. **Molla AM et al.** Rice powder electrolyte solution as oral therapy in diarrhoea due to *Vibrio cholerae* and *Escherichia coli*. *Lancet*, 1982, **1**: 1317–1319.
61. **Phillips AR.** Water and electrolyte losses in cholera. *Federation proceedings*, 1964, **32**: 705–712.
62. **Ribeiro HJ et al.** Treatment of acute diarrhoea with oral rehydration solutions containing glutamine. *Journal of the American College of Physicians*, 1994, **13**: 251–255.
63. **Maulen-Radovan I et al.** Safety and efficacy of a rice-based rehydration salt solution in the treatment of diarrhea in infants less than 6 months of age. *Journal of pediatric gastroenterology and nutrition*, 1994, **19**: 78–82.